II. REMARKS:

A. Status of the Claims

Claims 1-18 were originally filed with the case. An Office Action requesting that Applicants select a single species for examination was mailed on October 7, 2005. Applicants timely responded, electing the species of AIT-082. Another Restriction Requirement was mailed on January 26, 2006, asserting that the application claimed three patentably distinct inventions and requiring that Applicants elect an invention for examination. Applicants timely responded, electing the Group I invention, directed to a method of treating dry eye.

Claims 1-6 were rejected in the Office Action mailed May 17, 2006. In a Response to Office Action filed on November 17, 2006, claims 1, 5, and 6 were amended, claim 4 was cancelled, and claims 7-18 were withdrawn as being directed to a non-elected invention. Claims 1-3, 5 and 6 were rejected in the Final Office Action mailed on March 29, 2007. No claims were amended, cancelled or added in the Response to Final Office Action filed on August 29, 2007. A Notice of Appeal was timely filed on October 1, 2007, and a Request for Continued Examination was timely filed on April 4, 2008. All claims were rejected in a non-final Office Action mailed on June 18, 2008. Claim 1 was amended and no claims were cancelled or added in a Response to Office Action filed on August 18, 2008. All claims remain rejected in the non-final Office Action mailed on December 26, 2008. Claim 1 is amended and no claims are added or canceled herein. Thus, claims 1-3, 5 and 6 remain pending.

B. The Claims are Definite

The Action rejects claims 1-6 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out the subject matter of the invention. The Action states that the terms "ONO-2506" and "CB-1093" are indefinite for failing to set forth the intended compounds. Claim 1 is amended herein to include the chemical names of compounds ONO-2506 and CB-1093. It is believed that the amendment to claim 1 renders the definiteness rejection moot.

In light of the amendments to claim 1 submitted herewith, Applicants respectfully request that the definiteness rejection be withdrawn.

C. The Claims are Patentable Over Wallace in view of WO 00/32197 and further over Glaser and The Drugs of Future 1997

The Action rejects all claims as being obvious over Wallace in view of WO 00/32197 and further over Glaser (US 5,767,079) and The Drugs of Future 1997 (22(9)). Wallace is said to teach the use of neurotrophic factors for the treatment of a number of eye disorders, including dry eye. The Action acknowledges that Wallace lacks a teaching of AIT-082. WO 00/32197 is said to teach that AIT-082 is a well-known neurotrophic factor. Thus, the Action asserts that it would have been obvious for a person skilled in the art to use AIT-082 for the treatment of dry eye. Glaser is said to teach the use of transforming growth factor for the treatment of different ophthalmic disorders. The Action considers dry eye to be one of the disorders treated by the growth factor. Drugs of the Future is said to teach that AIT-082 is the first growth factor mimetic compound. According to the Action, it would have been

obvious to use a growth factor mimetic agent for the treatment of the disorders that are treated by growth factor. Applicants respectfully traverse.

Wallace appears to discuss compositions containing a neurotrophic factor and their use in the treatment of ocular disorders associated with ciliary ganglionic nerve cell degeneration. The neurotrophic factors discussed in Wallace are proteinaceous compounds characterized by having a pI in the range of 5.6 to 7.0 and a molecular weight of about 31.5 kD (Wallace, col. 2, lines 39-42). It is difficult to exploit peptide or protein molecules pharmaceutically due to bioavailability problems generally resident in the pharmaceutical administration of peptides (Spec. page 4, lines 11-13). Therefore, the methods of the present invention focus on the use of small molecule compounds that promote neuron regeneration or neurite outgrowth in a pharmaceutically acceptable vehicle to treat dry eye resulting from injury to corneal nerves. Wallace does not suggest the use of any compounds other than the proteinaceous neurotrophic factors themselves. That is, Wallace contains no suggestion to use small molecule compounds that promote neuron regeneration or neurite outgrowth would be useful in the compositions and methods described.

The Action argues that "there is no evidence of record to demonstrate that difference neurotrophic factors cannot be used for the treatment of dry eye syndrome," or that "the size of compounds with neurotrophic activity can influence their treatment ability for the treatment of dry eye." Applicants assert that the Action is missing the point of distinction. The compounds discussed in Wallace are proteins or peptides. Therefore, the difference between the compounds used in the methods of the present invention and those discussed in Wallace is more than size alone. The methods of the invention require topical administration of the composition to treat

dry eye. The skilled artisan is well aware of the difficulties associated with topical administration of proteins or peptides.

The Action takes the position that it would have been obvious to combine the teachings of WO 00/32917 with the teachings of Wallace because WO 00/32917 appears to discuss the use of neurotrophic factor stimulators to treat glaucomatous neuropathy and other retinal and optic nerve head degenerative diseases. Retinal and optic nerve head degenerative diseases are disorders occurring in the back of the eye. Dry eye resulting from injury to the cornea, however, is a disorder that occurs near the front of the eye. The Action states that there is no evidence to demonstrate that the dry eye can be treated differently depending on the location and cause of such disorder. The missing link in that argument is that WO 00/32917 does not discuss the treatment of dry eye, but rather the treatment of retinal and optic nerve head degenerative diseases. The Action has not provided any reason why the skilled artisan would jump from treatment of disorders affecting the tissues of the back of the eye, which do not include dry eye, to the treatment of dry eye, which occurs at the front of the eye.

WO 00/32917 does not suggest that the compounds described therein can be used to treat disorders affecting the front of the eye, such as dry eye resulting from injury to the cornea. It is well known to the skilled artisan that, in order to deliver compounds to the eye for treatment of tissues at the back of the eye, one must typically deliver the active agent directly to the tissues at the back of the eye via intravitreal or juxtascleral injection, or the like. Most known compounds do not reach the tissues at the back of the eye via administration to the front of the eye. This is especially true of large molecules, such as proteins.

The present Action adds two additional references to the obviousness rejection, but does not appear to provide any reason with respect to why the skilled artisan would combine the additional two references (Glaser and Drugs of the Future) with the references cited in the previous Action (Wallace and WO 00/32197).

Glaser appears to discuss treatment of certain ocular disorders by administering TGFβ. Peptides in the TGF-β family are known to regulate cell growth and differentiation and can both stimulate and inhibit cell proliferation depending largely on the cell type and environment. (Glaser, Col. 6, lines 43-46). It has been reported that TGF-β1 can seal the edge of surgical retinotomy in rabbits, stimulate collagen glycoprotein synthesis and cellular proliferation and migration involved in the wound healing process. (Glaser, Col. 6, line 66 to Col. 7, line 11). Glaser suggests administering TGF-β, preferably TGF-β2, in a method for significantly improving the ocular vision in retinal disorders of the mammalian eye. (Col. 7, lines 27-32).

The Action asserts that Glaser teaches that other growth factors which have wound healing and neurotrophic effect may also be used, pointing to Col. 2, lines 28-30. While the passage referenced does not mention the use of other growth factors, a passage in Col. 11 (beginning at line 62) does state that "Other growth factors which have <u>both</u> wound healing and neurotrophic effects can be applied in <u>certain</u> of these inventive treatments." (emphasis added). Glaser does not specify which of the "inventive treatments" described therein could be treated by the other growth factors mentioned. However, in light of the description of the function of TGF-β as regulating cell growth and either stimulating or inhibiting cell proliferation, the skilled artisan is likely to find it reasonable that such compounds could be

useful for treating retinal disorders, which are known to stem from cell proliferation, or possibly for aiding in wound healing, but not necessarily for treating dry eye. Moreover, Glaser cautions that administering TGF-β1 or TGF-β2 without any preexisting neovascularization may cause neovascularization to develop. (Col. 19, lines 3-5, emphasis added). It is well known that dry eye is not typically accompanied by neovascularization. This would amount to a teaching away with respect to the use of growth factors for the treatment of dry eye alone.

Drugs of the Future appears to discuss the compound AIT-082 and its use to inhibit age-related memory loss in mice. AIT-082 is described as having "neurotrophic-modulating activities." The compound was administered to the mice studied orally, via drinking water. While AIT-082 is also described as a "growth factor-mimetic agent," there is no suggestion within Drugs of the Future to administer the compound topically to the eye of a patient suffering from dry eye. Drugs of the Future further states that the compound induces the production of several growth factors. Combining that fact with the statement in Glaser that administering TGF-β1 or TGF-β2 without preexisting neovascularization may causer neovascularization to develop may further guide the skilled artisan away from the use of AIT-082 to treat dry eye.

In light of the foregoing arguments, Applicants respectfully request that the obviousness rejection based upon Wallace, WO 00/32917, Glaser and Drugs of the Future be withdrawn.

D. Conclusion

This is submitted to be a complete response to the outstanding Final Office Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Teresa J. Schultz #40,526/

Teresa J. Schultz
Reg. No. 40,526
Attorney for Applicants

ALCON RESEARCH, LTD.
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
(817) 551-4321

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